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SYNTHESIS OF NEW FUNCTIONAL DERIVATIVES OF PYRAZOLIDINE FROM 1-ACETYL-3-METHYL-5-NITROMETHYL-2-PHENYLPYRAZOLIDINE

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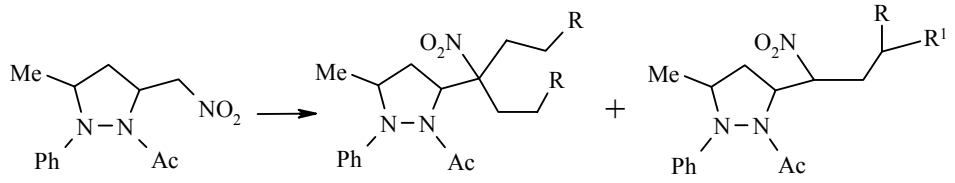
3-Nitromethylpyrazolidine reacts with derivatives of unsaturated acids and reducing agents with the formation of polyfunctional compounds of the pyrazolidine nucleus.

Keywords: 5-nitromethylpyrazolidine, Mannich reaction, Michael reaction, reduction of a nitro group.

We previously found a new method of directly introducing CH-acid radicals into the pyrazolidine molecule [1] on the surface of adsorbents without a solvent. Among others, a method of synthesizing pyrazolidine 5-nitromethyl derivatives was developed. In the present work further conversions of 1-acetyl-3-methyl-5-nitromethyl-2-phenylpyrazolidine (**1**) have been studied using the reactivity of both the methylene and the nitro groups.

In [1] conditions were found for the synthesis of nitro derivative **1** with a *cis*:*trans* isomers ratio of 1:4. After a small change to the method we succeeded in obtaining a diastereoselective course for the process on neutral aluminum oxide and the isomer ratio of compound **1** was ~1:100 according to data of ^{1}H NMR spectra. In this way we obtained predominantly one diastereomeric pair of *trans* structure. Attempts to introduce the obtained nitro derivative **1** into a Michael reaction with derivatives of unsaturated acids under the usual conditions with a basic catalyst (triethylamine) were unsuccessful. In view of our positive experiment using the method of carrying out the reaction on the surface of an adsorbent without a solvent [1], we carried out a series of trial experiments and discovered that the Michael reaction with acrylonitrile proceeds best of all at room temperature on basic aluminum oxide containing 20% adsorbed KF. After 48 h the initial compound **1** reacted completely with the formation of product **2** by addition of two molecules of acrylonitrile.



2 R = CN; **3a–c** R = COOMe; **b** R^1 = H; **c** R^1 = Me

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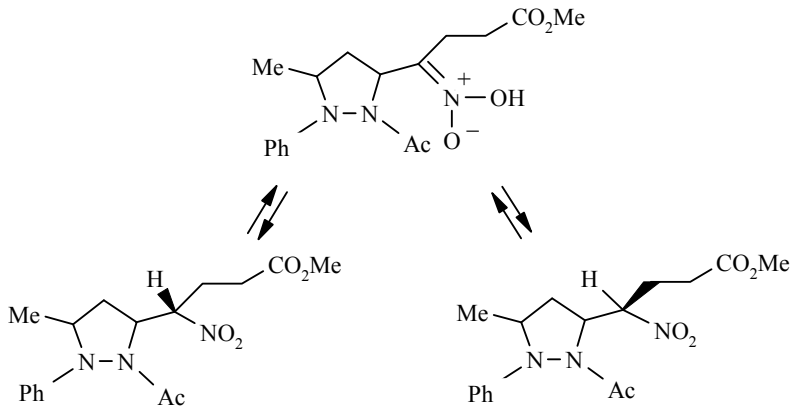
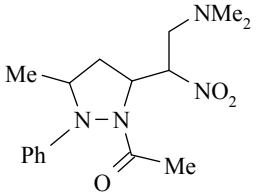
The structure of bisadduct **2** was confirmed by data of IR, ^{1}H NMR, and mass spectroscopy (see Experimental). Attempts to obtain the monoadduct of acetonitrile proved to be in vain. On reducing the amount of acrylonitrile a mixture is formed of compound **2** with the initial **1** and on changing the adsorbent conversion did not occur. The interaction of nitro compound **1** with methyl acrylate was effected under the same conditions. After 30 h, according to TLC, the initial pyrazolidine had reacted completely. From the reaction mixture both the bisadduct **3a** and also two isomeric monoadducts **3b,b'**, were obtained in a ratio of 5:1 according to data of ^{1}H NMR spectra. On standing the mixture of isomers **3b,b'** in ethyl acetate solution the isomer ratio changed. After 10 days isomer **3b'** disappeared completely and the more stable isomer **3b** accumulated. Probably the conversion occurs through the *aci* form of the nitro compound.



3b,b'

The interaction of compound **1** with methyl methacrylate was determined to a significant extent by steric factors. The sole compound **3c** obtained in 31% yield has 4 asymmetric centers and is a mixture of diastereomeric monoadducts, which is indicated by the multifold doubling of signals in the ^{1}H NMR spectrum. These isomers are liquids and have very low R_f values.

Attempts to carry out an aldol condensation of compound **1** with aromatic aldehydes were unsuccessful. The optimum conditions for carrying out the similar process, the Mannich reaction, proved to be the use of bis(dimethylamino)methane in acetonitrile solution. According to GLC data the obtained Mannich base **4** was a mixture of two substances in a ratio of 1:6. Both compounds have the same characteristics of IR and ^{1}H NMR spectra but somewhat different mass-spectral decomposition, which suggests that these are different diastereomeric pairs.



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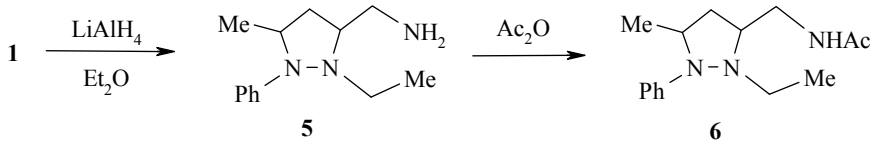
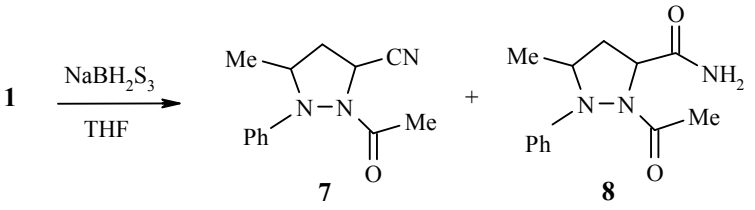
To reduce both the amide and the nitro group it was most expedient to use lithium aluminum hydride. Nitro compound **1** was completely converted by this into 3-aminomethyl-2-ethyl-5-methyl-1-phenylpyrazolidine (**5**) in 91% yield. The hydrochloride of the obtained amine proved to be extremely hygroscopic so the amine was identified additionally as the acetyl derivative **6**.



Incomplete reduction of the nitro group with sulfided sodium borohydride $NaBH_2S_3$, used to reduce nitro groups in nitroalkanes [2], led to the formation of two substances, 1-acetyl-5-cyano-3-methyl-2-phenylpyrazolidine (44%) (**7**) and 1-acetyl-5-carbamoyl-3-methyl-2-phenylpyrazolidine (**8**), inaccessible by other methods.



It is therefore possible to synthesize new mono- and bifunctional derivatives of pyrazolidines from pyrazolidine nitromethyl derivatives.

EXPERIMENTAL

The IR spectra of compounds were measured on UR 20 and Specord IR 75 instruments in KBr disks or nujol, and ^{1}H NMR spectra on a Varian XR 400 instrument (400 MHz) in $CDCl_3$, internal standard was TMS. Mass spectra were recorded on a Hewlett-Packard 5873 chromato-mass spectrometer (ionization energy 70 eV), with a HP 6890 chromatograph. A check on the progress of reactions and the purity of the substances obtained was effected by TLC on Silufol UV 254 plates in the system petroleum ether–ethyl acetate, 1:1, visualizing with alcoholic $FeCl_3$ solution, iodine vapor, or aqueous potassium permanganate solution. Chromatographic purification of the compounds obtained was carried out by flash chromatography on a dry column [3] of L5/40 silica gel, eluent was petroleum ether–ethyl acetate. 2:1.

***trans*-1-Acetyl-5-hydroxy-3-methyl-2-phenylpyrazolidine** was obtained by the method of [4].

***trans*-1-Acetyl-3-methyl-5-nitromethyl-2-phenylpyrazolidine (1).** A solution of 1-acetyl-5-hydroxy-3-methyl-2-phenylpyrazolidine (0.5 g, 2.5 mmol) in benzene (5 ml) was added to calcined neutral aluminum oxide (5 g). The benzene was distilled off on the rotary evaporator to obtain a dry powder. Nitromethane (0.2 ml) was added to the mixture, shaken vigorously for several minutes, then heated on a sand bath for 48 h at 60-70°C, periodically adding nitromethane (about 0.1 ml). After the end of the reaction (check by TLC, benzene–ethyl acetate, 1:1), the reaction mixture was extracted with chloroform in a Soxhlet extractor. The extract was evaporated in vacuum, and the residue recrystallized from ether. Yield 0.15 g (25%); mp 88°C. IR spectrum, ν, cm^{-1}: 1680 (NCO), 1500, 1385 (NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (3H, d, *J* = 6.8, 3-CH_3); 1.93 (1H, m, H-4); 2.05 (3H, s, CH_3CO); 2.21 (1H, m, H-4); 4.25 (1H, m, H-3); 4.25 (1H, m, CH_2NO_2); 4.94 (1H, m, H-5); 4.95 (1H, m, CH_2NO_2); 6.92 (3H, m, 2-C_6H_5); 7.31 (2H, m, 2-C_6H_5). Found, %: C 59.52; H 7.13. $C_{13}H_{17}N_3O_2$. Calculated, %: C 59.32; H 6.46.

1-Acetyl-5-[bis(2-cyanoethyl)nitromethyl]-3-methyl-2-phenylpyrazolidine (2). A solution of nitromethylpyrazolidine **1** (0.1 g, 0.38 mmol) in benzene (2 ml) was applied to calcined basic aluminum oxide containing 20% KF [5] (1 g). The benzene was distilled off on the rotary evaporator to obtain a dry powder. Acrylonitrile (0.2 ml) was added to the mixture, which was shaken vigorously for several minutes, after which

the mixture was stored for 48 h at room temperature. The adduct was isolated by flash chromatography on a dry column, collecting the fraction with R_f 0.5. Yield 0.06 g (50%); mp 135°C. IR spectrum, ν, cm^{-1}: 1680 (NCO), 1550 (NO_2), 2260 (CN). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, d, *J* = 6.8, 3-CH_3); 1.92 (1H, m, H-4); 2.12 (3H, s, CH_3CO); 2.25 (1H, m, H-4); 2.43 (4H, m, 5-CH_2-β); 2.63 (4H, m, CH_2-α); 4.24 (1H, m, H-3); 4.92 (1H, m, H-5); 6.75 (2H, m, 2-C_6H_5); 6.92 (1H, m, 2-C_6H_5); 7.35 (2H, m, 2-C_6H_5). Found, %: C 60.73; H 6.39. $C_{19}H_{23}N_5O_3$. Calculated, %: C 61.0; H 6.32.

1-Acetyl-5-[bis(2-methoxycarbonylethyl)nitromethyl]-3-methyl-2-phenylpyrazolidine (3a) and 1-Acetyl-5-(3-methoxycarbonyl-1-nitropropyl)-3-methyl-2-phenylpyrazolidines (3b,b'). Methyl acrylate (0.2 ml) was added to nitromethylpyrazolidine **1** (0.1 g, 0.38 mmol) applied to aluminum oxide containing KF (see previous procedure), the mixture was shaken vigorously for several minutes, and stored for 30 h at room temperature. The monoadduct **3b** was isolated by flash chromatography on a dry column, collecting the fraction with R_f 0.8. Yield 0.05 g (37%); mp 78°C. IR spectrum, ν, cm^{-1}: 1680 (NCO), 1560 (NO_2), 1740 (CO_2CH_3). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, d, *J* = 6.8, 3-CH_3); 1.92 (1H, m, H-4); 1.95 (2H, m, CH_2-β); 2.01 (3H, s, CH_3CO); 2.25 (1H, m, H-4); 2.45 (2H, m, CH_2-α); 3.64 (3H, s, OCH_3); 4.18 (1H, m, H-3); 4.35 (1H, m, $CHNO_2$); 4.90 (1H, m, H-5); 6.92 (3H, m, 2-C_6H_5); 7.35 (2H, m, 2-C_6H_5). Found, %: C 60.82; H 6.91, *m/z* 349 $[M]^+$. $C_{17}H_{23}N_3O_5$. Calculated, %: C 59.51; H 6.52, M 349.

A second fraction with R_f 0.5 (mixture of isomers **3a** and **3b'**) was analyzed by ^1H NMR and chromato-mass spectrometry.

Compound 3a. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, d, *J* = 6.8, 3-CH_3); 1.93 (1H, m, H-4); 1.97 (4H, m, CH_2-β); 2.03 (3H, s, CH_3CO); 2.23 (1H, m, H-4); 2.43 (4H, m, CH_2-α); 3.65 (6H, s, OCH_3); 4.23 (1H, m, H-3); 4.94 (1H, m, H-5); 6.88 (2H, m, 2-C_6H_5); 7.33 (3H, m, 2-C_6H_5). Mass spectrum, *m/z* (*I*, %): 388 (41) $[M\text{-}HNO_2]^+$; 345 (100) $[M\text{-}HNO_2\text{-}CH_3CO]^+$.

Compound 3b'. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, d, *J* = 6.8, 3-CH_3); 1.93 (1H, m, H-4); 1.95 (2H, m, CH_2-β); 2.00 (3H, s, CH_3CO); 2.25 (1H, m, H-4); 2.45 (2H, m, CH_2-α); 3.63 (3H, s, OCH_3); 4.19 (1H, m, H-3); 4.35 (1H, m, $CHNO_2$); 4.89 (1H, m, H-5); 6.78 (3H, m, 2-C_6H_5); 7.29 (2H, m, 2-C_6H_5).

1-Acetyl-3-methyl-5-(2-methyl-3-methoxycarbonyl-1-nitropropyl)-2-phenylpyrazolidine (3c) was obtained by the previous method using methyl methacrylate (0.2 ml), and collecting the fraction with R_f 0.6. Yield 0.043 g (31%); mp 149°C. Found, %: C 62.89; H 7.71. $C_{18}H_{25}N_3O_5$. Calculated, %: C 61.52; H 6.78.

1-Acetyl-5-(2-dimethylamino-1-nitroethyl)-3-methyl-2-phenylpyrazolidine (4). Bisdimethylamino-methane (1 ml) was added to a solution of compound **1** (0.1 g, 0.38 mmol) in acetonitrile (5 ml), and left for 24 h. The solvent was distilled off, the residual thick oil was rubbed with a small quantity of ether, and recrystallized from ether. Yield 0.05 g (41%); mp 152-155°C. IR spectrum, ν, cm^{-1}: 1680 (NCO), 1550, 1360 (NO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.21 (3H, d, *J* = 6.8, 3-CH_3); 1.91 (1H, m, H-4); 2.15 (3H, s, CH_3CO); 2.25 (1H, m, H-4); 2.26 [6H, s, $N(CH_3)_2$]; 2.41 (2H, m, CH_2N); 4.22 (1H, m, $CHNO_2$); 4.25 (1H, m, H-3); 4.94 (1H, m, H-5); 6.92 (3H, m, 2-C_6H_5); 7.35 (2H, m, 2-C_6H_5). Found, %: C 56.39; H 7.81; *m/z* 320 $[M]^+$. $C_{16}H_{24}N_4O_3$. Calculated, %: C 57.0; H 7.50; M 320.

3-Aminomethyl-2-ethyl-5-methyl-1-phenylpyrazolidine (5). A solution of compound **1** (0.263 g, 1 mmol) in ether (10 ml) was added with stirring to $LiAlH_4$ (0.3 g, 8 mmol) in absolute ether (15 ml). The reaction mixture was boiled for 8 h, water (0.5 ml) was added carefully, the precipitated hydroxide was filtered off, and washed with ether. The combined ether fractions were dried over magnesium sulfate, and the ether distilled off. Compound **5** (0.2 g, 91%) was obtained as a yellow oil. IR spectrum, ν, cm^{-1}: 3270, 3380 (NH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.85 (2H, s, NH_2); 1.13 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 1.22 (3H, d, *J* = 6.8, 3-CH_3); 1.85 (1H, m, H-4); 2.14 (1H, m, H-4); 2.27 (2H, m, CH_2NH_2); 2.83 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 3.14 (1H, m, H-3); 3.63 (1H, m, H-5); 6.64 (1H, m, C_6H_5); 6.94 (2H, m, C_6H_5); 7.34 (2H, m, C_6H_5). Found: *m/z* 219 $[M]^+$. $C_{13}H_{21}N_3$. Calculated: M 219.

3-Acetylaminomethyl-2-ethyl-5-methyl-1-phenylpyrazolidine (6). Acetic anhydride (0.1 ml) was added to a solution of compound **5** (0.1 g, 0.45 mmol) in benzene (10 ml), the mixture boiled for 3 h, and the benzene and acetic anhydride were distilled off. The acetylaminomethylpyrazolidine **6** (0.1 g, 84%) was

obtained of mp 77°C. IR spectrum, ν, cm^{-1}: 1680 (NCO). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.13 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 1.44 (3H, d, *J* = 6.8, 3-CH_3); 1.75 (3H, s, CH_3CO); 1.86 (1H, m, H-4); 2.26 (2H, m, H-4); 2.74 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 2.86 (2H, m, $C\underline{H}_2N$); 3.35 (1H, m, H-3); 3.66 (1H, m, H-5); 6.63 (1H, m, C_6H_5); 6.92 (2H, m, C_6H_5); 7.33 (2H, m, C_6H_5). Found, %: C 68.92; H 8.83. $C_{15}H_{23}N_3O$. Calculated, %: C 69.0; H 8.81.

1-Acetyl-5-cyano-3-methyl-2-phenylpyrazolidine (7) and 1-Acetyl-5-carbamoyl-3-methyl-2-phenylpyrazolidine (8). Tetrahydrofuran (5 ml) was added to a mixture of $NaBH_4$ (0.0378 g, 1 mmol) and sulfur (0.1 g, 3 mmol) with stirring in a current of inert gas. Then a solution of nitromethylpyrazolidine **1** (0.263 g, 1 mmol) in THF (5 ml) was added. The reaction mixture was boiled until disappearance of the initial pyrazolidine (4 h), after which 10% NaOH (15 ml) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 ml). The extract was dried over magnesium sulfate, and evaporated. The residue was chromatographed on a dry column of silica gel, collecting the fraction of R_f 0.8. Cyanopyrazolidine **7** (0.1 g, 43.6%) was obtained as a dark red substance of mp 55°C. IR spectrum, ν, cm^{-1}: 1680 (NCO), 2300 (CN). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.35 (3H, d, *J* = 6.8, 3-CH_3); 1.95 (1H, m, H-4), 2.04 (3H, s, CH_3CO); 2.24 (1H, m, H-4); 4.24 (1H, m, H-3); 5.03 (1H, m, H-5); 6.92 (3H, m, C_6H_5); 7.34 (2H, m, C_6H_5). Found: *m/z* 229 $[M]^+$. $C_{13}H_{15}N_3O$. Calculated: M 229.

A second fraction with R_f 0.4 was compound **8** of mp 107°C according to mass spectroscopy. Found: *m/z* 247 $[M]^+$. $C_{13}H_{17}N_3O_2$. Calculated: M 247.

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